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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,665	09/19/2005	Adrian Merlo	2005_1392A	3706

513 7590 06/11/2010

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ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
06/11/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/549,665
Filing Date: September 19, 2005
Appellant(s): MERLO ET AL.

William Schmidt, II
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 5/24/2010 appealing from the Office action mailed 10/20/2009.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Pending claims: 1-13 and 17-30

Withdrawn claims: 1-13 and 21-28

Rejected claims: 17-20 and 29-30

Cancelled claims: 14-16

Appealed claims: 17-20 and 29-30.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

WO 92/18536	VISSER	10-1992
US 5,750,646	COY	5-1998

Li *et al.* (*Bioconjugate Chem.*, 2002, 13(4), p. 721-8).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Visser *et al.* (WO 92/18536).

Visser discloses methods for detecting and localizing tissues having neurokinine 1 receptors in the body of a warm-blooded living being by administration of a labeled small peptide having selective affinity to neurokinine 1 receptor, and by then radioassaying said being. The method also relates to therapeutic treatment of tumors (abstract). Diagnosis and therapy of gliomas are disclosed (page 1, lines 29+). A peptide having an affinity for neurokinine 1 receptors is labeled with (a) a detectable metal isotope selected from the group consisting of In-111, etc., said metal isotope being attached to said peptide via a suitable linker capable of reacting with an amino

group, preferably a terminal amino group of said peptide, and having a chelating group for chelating said metal isotope (page 2, lines 19-28). The labeled peptide is derived from the following formula (page 4), including substance p and derivatives thereof in examples 1-5:

$$R_1\text{-}(A_1)_m\text{-}A_2)_n\text{-}A_3)_o\text{-}Pro)_p\text{-}A_4)_q\text{-}A_5\text{-}Phe\text{-}A_6\text{-}A_7\text{-}A_8\text{-}Met(O)_s\text{-}R_2 \quad (I)$$

wherein all of the symbols m, n, o, p and q are 1, or all but one of the symbols m, n, o, p and q are 1 and the remaining symbol is 0;
R_1 is a hydrogen atom or a C_1-C_4 alkylcarbonyl group;
R_2 is an amino group, a hydroxy group or a C_1-C_4 alkoxy group;
A_1 is Arg, Gly or 5-oxo-Pro (pGlu);
A_2 is Pro or ß- Ala;
A_3 is Lys or Asp;
A_4 is Gln, Asn or 5-oxo-Pro;
A_5 is Gln, Lys, Arg, N-acylated Arg or 5-oxo-Pro;
or wherein A_5 together with A_3 forms a cystine moiety;
A_6 is Phe or Tyr;
A_7 is Gly, Sar or Pro;
A_8 is Leu or Pro; and
s is 0, 1 or 2;
or a Tyr^0 derivative thereof.

A suitable linker for attaching a metal isotope to the small peptide is provided with a chelating group, e.g. DOTA, etc (page 5, line 30-page 6, line 35). Pharmaceutical compositions including carrier, etc. are disclosed (page 7, lines 1-11).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Visser *et al.* (WO 92/18536) in view of Coy *et al.* (US 5,750,646).

Visser discloses radiolabelled chelator-substance p analogue conjugates for diagnosis and therapy of tumor displaying neurokinine 1 receptors, as set forth above.

With respect to Applicant's elected species, conjugate DOTA-[Thi^{8},$Met(O_2)^{11}$]-Substance P, Visser does not specifically recite substitution of Thi for Phe at position 8 of the instantly claimed amino acid sequence. Rather, Visser teaches Phe or Tyr at this position (A_6 in the notation of Visser).

However, nonnatural amino acids such as thienylalanine are known in the art to be interchangeable with Phe in similar peptide systems as shown by Coy.

Coy discloses linear peptides which are analogues of naturally occurring biologically active peptides having an active site and a binding site responsible for binding of the peptide to a receptor on a target cell (see abstract). Substance P and

related peptides are disclosed (see column 20 and Table 1). A bradykinin antagonist of formula Q^0-A^1-A^2-A^3-A^4-Gly-A^5-A^6-A^7-A^8-A^9-Z^{10} is disclosed, wherein A^8 is Phe, p-X-Phe, or thienylalanine (see claim 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute Thi for Phe at position 7 and/or 8 of the substance P analogue-chelators disclosed by Visser. The Supreme Court in KSR International Co. v. Teleflex Inc., 550 U.S. ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. One such rationale includes the simple substitution of one known element for another to obtain predictable results. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. See MPEP 2143. In the instant case, the substituted components (Thi and Phe) and their functions were known in the art at the time of the instant invention. For example, Coy teaches Phe and Thi to be interchangeable as a given residue in bradykinin antagonist peptides. One of ordinary skill in the art could have substituted one known amino acid for another, and the results of the substitution would have been predictable, that is a biologically active peptide having an active site and a binding site responsible for binding of the peptide (substance p analogue) to a receptor (e.g. neurokinine 1 receptor), especially as Coy is concerned with maintaining binding as in the naturally occuring peptide (abstract).

Claims 17-20 and 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Visser *et al.* (WO 92/18536) in view of Li *et al.* (*Bioconjugate Chem.*, 2002, 13(4), p. 721-8).

Visser discloses methods for detecting and localizing tissues having neurokinine 1 receptors in the body of a warm-blooded living being by administration of a labeled small peptide having selective affinity to neurokinine 1 receptor, and by then radioassaying said being. The method also relates to therapeutic treatment of tumors (abstract). Diagnosis and therapy of gliomas are disclosed (page 1, lines 29+). A peptide having an affinity for neurokinine 1 receptors is labeled with (a) a detectable metal isotope selected from the group consisting of In-111, etc., said metal isotope being attached to said peptide via a suitable linker capable of reacting with an amino group, preferably a terminal amino group of said peptide, and having a chelating group for chelating said metal isotope (page 2, lines 19-28). The labeled peptide is derived from the following formula (page 4), including substance p and derivatives thereof in examples 1-5:

R_1-$(A_1)_m$-$A_2)_n$-$A_3)_o$-Pro)$_p$-$A_4)_q$-A_5-Phe-A_6-A_7-A_8-Met(O)$_s$-R_2 (I)

wherein all of the symbols m, n, o, p and q are 1, or all but one of the symbols m, n, o, p and q are 1 and the remaining symbol is 0;
R_1 is a hydrogen atom or a C_1-C_4 alkylcarbonyl group;
R_2 is an amino group, a hydroxy group or a C_1-C_4 alkoxy group;
A_1 is Arg, Gly or 5-oxo-Pro (pGlu);
A_2 is Pro or β- Ala;
A_3 is Lys or Asp;
A_4 is Gln, Asn or 5-oxo-Pro;
A_5 is Gln, Lys, Arg, N-acylated Arg or 5-oxo-Pro;
or wherein A_5 together with A_3 forms a cystine moiety;
A_6 is Phe or Tyr;
A_7 is Gly, Sar or Pro;
A_8 is Leu or Pro; and
s is 0, 1 or 2;
or a Tyr^0 derivative thereof.

See also compound 2, page 4. A suitable linker for attaching a metal isotope to the small peptide is provided with a chelating group, e.g. DOTA, etc (page 5, line 30-page 6, line 35). Pharmaceutical compositions including carrier, etc. are disclosed (page 7, lines 1-11). With regard to preparation of substance p analogue-chelator conjugates, Visser discloses solid-phase synthesis of peptide, and then reacting Lysine-protected substance p and DTPA-dianhydride. Labelling of DTPA-substance p is achieved by mixing with In-III chloride solution (page 10).

Visser does not disclose reaction of protected substance p analogue with DOTA(^{t}Bu)$_3$, as claimed. It is for this reason that Li is joined.

Li discloses attachment of DOTA to the D-Tyr^1 residue of somatostatin receptor D-TYr-^{1}-octreotate, allowing radiolabeling with radiohalogens and radiometals

(abstract). Solid phase peptide synthesis was followed using Fmoc methodology. DOTA-tris-(tert-butyl ester) was activated and coupled to Fmoc-protected amino acids (page 722, right column).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute DOTA(^{t}Bu)$_3$ as a functional equivalent reactant disclosed in the reaction coupling a chelator to peptide in Visser. The Supreme Court in KSR International Co. v. Teleflex Inc., 550 U.S. ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. One such rationale includes the simple substitution of one known element for another to obtain predictable results. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. See MPEP 2143. In the instant case, the substituted components (DOTA/DTPA prochelators) and their functions were known in the art at the time of the instant invention. For example, Visser shows DTPA anhydride as a reactant for coupling chelator to peptide using Fmoc protected amino acids. Li shows DOTA(^{t}Bu)$_3$ as a reactant for coupling chelator to peptide using Fmoc protected amino acids. One of ordinary skill in the art could have substituted one known reactant (prochelator) for another, and the results of the substitution would have been predictable, that is conjugation of a chelator to substance p analogue.

(10) Response to Argument

With regard to the rejection of claims 17-20 under 35 U.S.C. 102(b) as being anticipated by Visser (WO 92/18536), Appellant argues on pages 11-12 of the Brief that the claimed invention relates to a conjugate of a substance P analogue and a chelator molecule and has the structure of formula II or having at least one of the modifications a)-f) in the amino acid sequence, and that it was surprisingly found that the conjugates of the claimed invention are much more effective than DOTAOC, radiolabeled substance P, substance P analogues, saporin or other small radio-labelled peptides with or without chelating agent in targeting and treatment of tumors, especially brain tumors. Appellant asserts that it was also surprisingly found that metal complex formation was achieved quickly, that the claimed complexes possess an unexpectedly high serum-half-life time without decreasing the binding affinity to the neurokinine 1 receceptor to an undesired extent.

This is not found to be persuasive. It is first noted that the reference has been applied under 35 U.S.C. 102(b), therefore allegation of unexpected results is not sufficient to overcome the rejection. In addition, attention is drawn to MPEP 716.02(d). Allegation of unexpected results must be commensurate in scope with the claimed invention. Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed

to see if the results occur over the entire claimed range. *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980). In the instant case, the claims are drawn to a variety of conjugates of formula II, including modifications a)-f). However, the specification provides data with respect to serum stability shown only ^{111}In-DOTAGA-[Thi^{8},Met(O$_2$)^{11}]-Substance P in comparison to ^{111}In-DOTAGA-Substance P in Example C3. Data with regard to binding affinity to NK-1 receptors is provided at Example C4, comparing a few sequences of the instant claims with substance P and ^{111}In-DOTAGA-Substance P. However, some of the claimed sequences appear to show increased receptor binding, and some appear to show decreased receptor binding based on IC_{50} values. Accordingly, the claims are drawn to a number of different peptide sequence modifications, but the allegation of unexpected results, serum stability, is shown only for a single compound, and the results with respect to binding affinity show do not show a correlation between improved properties and the claimed sequences. The allegation of unexpected results is not commensurate in scope with the claimed invention.

In addition, See MPEP 716.02(e). The claimed invention must be compared with the closest prior art. An affidavit or declaration under 37 CFR 1.132 must compare the claimed subject matter with the closest prior art to be effective to rebut a *prima facie* case of obviousness. *In re Burckel*, 592 F.2d 1175, 201 USPQ 67 (CCPA 1979). "A comparison of the *claimed* invention with the disclosure of each cited reference to determine the number of claim limitations in common with each reference, bearing in mind the relative importance of particular limitations, will usually yield the closest single prior art reference." *In re Merchant*, 575 F.2d 865, 868, 197 USPQ 785, 787 (CCPA

1978) (emphasis in original). Where the comparison is not identical with the reference disclosure, deviations therefrom should be explained, *In re Finley*, 174 F.2d 130, 81 USPQ 383 (CCPA 1949), and if not explained should be noted and evaluated, and if significant, explanation should be required. *In re Armstrong*, 280 F.2d 132, 126 USPQ 281 (CCPA 1960) (deviations from example were inconsequential). In the instant case, serum stability studies are performed comparing the compound ^{111}In-DOTAGA-[Thi^{8},Met(O$_2$)^{11}]-Substance P with ^{111}In-DOTAGA-Substance P in Example C3, and . binding affinity to NK-1 receptor studies are provided comparing a few of the claimed sequences to Substance P and ^{111}In-DOTAGA-Substance P. However, Visser shows conjugation of sequences which may be considered to be closer prior art than native Substance P, such as example compound 2 on page 4. This compound is directly corresponding with at least modification b) of the instant claims, and can be considered to be closer prior art than the native Substance P sequence.

Appellant further argues on pages 12-13 of the Response that Visser discloses a method for detecting and localizing tissues having neurokinine 1 receptors, and that Visser teaches general formula 1, amounting to several million different combinations. Appellant argues that the claimed invention encompasses only one of these millions of compounds, namely DOTA-Arg^{1}-Pro^{2}-Lys^{3}-Pro^{4}-Gln^{5}-Gln^{6}-Phe^{7}-Phe^{8}-Gly^{9}-Leu^{10}-Met(O)-NH2. Appellant contends that one cannot find a hint in Visser that would make him select the claimed compounds, and that the examples of Visser only describe DTPA as the chelator. Appellant asserts that even if the generic formula I of Visser in

theory includes the above compound, it fails to particularly teach the species claimed in the present invention.

This is not found to be persuasive. A generic chemical formula can anticipate a claimed species covered by the formula when the species can be "at once envisaged" from the formula. See MPEP 2131.02. When the compound is not specifically named, but instead it is necessary to select portions of teachings within a reference and combine them, e.g., select various substituents from a list of alternatives given for placement at specific sites on a generic chemical formula to arrive at a specific composition, anticipation can only be found if the classes of substituents are sufficiently limited or well delineated. *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990). If one of ordinary skill in the art is able to "at once envisage" the specific compound within the generic chemical formula, the compound is anticipated. One of ordinary skill in the art must be able to draw the structural formula or write the name of each of the compounds included in the generic formula before any of the compounds can be "at once envisaged." One may look to the preferred embodiments to determine which compounds can be anticipated. *In re Petering*, 301 F.2d 676, 133 USPQ 275 (CCPA 1962). In the instant case, the sequence of substance p is well known in the art to be: Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met. From the disclosure of Visser, one of ordinary skill would only need to select $MetO_2$ for Met from Visser's generic structure based on the known sequence of substance P to arrive at Applicant's claimed structure. Since the sequence of substance P is well known, one would immediately envisage making a selection of $MetO_2$ based on Visser's genus of three possible variations at this

position (Met, MetO or $MetO_2$). It is further noted that example compound 2 of Visser directly encompasses modification b) of the instant claims (e.g. Sar at position 9). Or as another example, one would immediately envisage making one of three selections for A_7 (e.g. Gly for Sar) for compound 2 of Visser. Likewise DOTA and DTPA are such commonly exchangeable chelators in the diagnostic arts such that one would readily envisage selection of one or the other, based upon Visser's disclosure that either chelator from a limited number of very well known chelators are suitable (claim 5 of Visser).

With regard to the rejection of claims 17-20 under 35 U.S.C. 103(a) as being unpatentable over Visser (WO 92/18536) in view of Coy (US 5,750,646), Appellant argues on pages 13-14 of the Brief that Coy fails to remedy the deficiencies of Visser set forth above. Appellant asserts that Coy mentions that non-natural amino acids, such as Thi are interchangeable with Phe, but that since Visser fails to teach all other limitations of the present invention, combining the teachings of the references do not lead a person skilled in the art to the subject matter of the claimed invention.

This is not found to be persuasive. Response to arguments drawn to the Visser reference are applied as above.

With regard to the rejection of claims 17-20, 29 and 30 under 35 U.S.C. 103(a) as being unpatentable over Visser (WO 92/18536) in view of Li *et al.* (*Bioconjugate Chem.*, 2002, 13(4), p. 721-8), Appellant argues on pages 14-15 of the Brief that Li fails to remedy the deficiencies of Visser set forth above.

This is not found to be persuasive. Response to arguments drawn to the Visser reference are applied as above.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Michael G. Hartley/

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